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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/663,497	MCINTIRE ET AL.	
	Examiner	Art Unit	
	Sarae Bausch	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,7,8 and 20-23* is/are pending in the application.

4a) Of the above claim(s) *2 and 3* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4, 7-8, 20-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Currently, claims 1-4, 7-8 and 20-23 are pending in the instant application. Claims 5-6 and 9-19 have been canceled. Claims 2-3 are withdrawn and claims 20-23 have been added. This action is written in response to applicant's correspondence submitted 07/17/2007. All the amendments and arguments have been thoroughly reviewed but were found insufficient to place the instantly examined claims in condition for allowance. The following rejections are either newly presented, as necessitated by amendment, or are reiterated from the previous office action. Any rejections not reiterated in this action have been withdrawn as necessitated by applicant's amendments to the claims. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. **This action is Final.**

Withdrawn Rejections

2. The rejections of claim 8, under 35 U.S.C. 112, second paragraph, made in section 9, page 3 of the previous office action mailed 09/01/2006, is withdrawn in view of the amendment to the claims.

Amendment to the Specification

3. It is noted that the amendment to the specification, filed 12/20/2006 does not comply with 37 CFR 1.121, as it recites "replace paragraphs 137-138 on page 11 of the specification", however paragraphs 137-138 are located on page 37 and not page 11 of the specification. However, since it is clear that paragraphs 137 and 138 are to be replaced and to expedite

prosecution, the amendment to the specification has been entered. Applicant is reminded that in amendments submitted to the office must comply with 37 CFR 1.121.

New Grounds of Rejection- Necessitated by Amendment to the Claims

Claim Rejections - 35 USC § 112- New Matter

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claim 23 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is newly presented, necessitated by the newly added claim.

Newly added claim 23 with the recitation of "a probe that specifically binds under stringent conditions to a polymorphism in exon 3 of TIM-1 gene" is not supported in the specification and raises the issue of new matter. The specification teaches four polymorphisms within exon 3 of TIM-1, SEQ ID No. 37-40 (see paragraph 37, page 9). The specification teaches hybridization patterns of variant sequences using oligonucleotide probes immobilized on a solid support (see paragraph 56, page 14) and teach hybridization under stringent conditions (see paragraph 57, page 15). The specification teaches the arrays may comprise probes specific for one two three or more TIM alleles, TIM-1, TIM-2, TIM-3, TIM-4 or combination thereof and teach the probes specifically bind to the allele of interest (see paragraph 59, page 15), however

the specification does not teach probes specific for "any" polymorphism in exon 3 of the TIM-1 gene, to which the claim is drawn. The specification only teaches four polymorphism within exon 3 of the TIM-1 gene and does not teach probes that specifically bind to any polymorphism within exon 3. The specification does not provide support for a probe that hybridizes under stringent conditions to a polymorphism in exon 3 of the TIM-1 gene. There is no support in the specification to use a probe to specifically bind to any polymorphism within exon 3 of TIM-1 gene.

Claim Rejections - 35 USC § 112-Enablement

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1, 4, 7-8 and 20-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification while being enabling for a method for determining a Caucasian's predisposition to atopy protection by detecting the presence of the homozygous polymorphism of 157insMTTTVP (polymorphism 1, SEQ ID No. 22), of TIM-1 in a hepatitis virus A positive Caucasian individual, wherein the presence of the MTTTVP insertion is indicative of a Caucasian's predisposition to protect against atopy, does not reasonably provide enablement for a method for the diagnosis of an individual's predisposition to any atopic immunological disorder by analyzing for the presence of any TIM-1 polymorphism. This rejection was previously

presented in section 11 of the previous office action mailed 09/01/2006 and has been rewritten to accommodate the amendment to the claims and the newly added claims 20-23.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims

The claims are drawn to a method for the diagnosis of an individual's predisposition to an atopic immunological disorder by analyzing the presence of at least one TIM-1 polymorphism wherein the presence of the polymorphism is indicative of an individual's predisposition to develop an atopic immunological disorder. The claims are further drawn to a method of contacting a biological sample with a probe that specifically binds to the nucleic acid sequence of MTTTVP or a polymorphism in exon 3 of TIM-1 gene and further comprising the step of analyzing an individual for the presence of hepatitis A virus seropositivity.

The rejected claims encompass analysis of a human. The rejected claims encompass any type of atopic immunological disorder and detection of any polymorphism in TIM-1.

The nature of the claims requires knowledge of a correlation between detection of the presence of a TIM-1 polymorphism and predisposition to develop an atopic immunological disorder.

Guidance in the Specification and Working Examples

The specification asserts that polymorphisms in the human TIM-1 gene and exposure to Hepatitis A Virus(HAV) are shown to be associated with protection from the development of immunological disorders, such as atopy. The specification asserts that a common polymorphism of TIM-1 in major human population has an insertion at position 157, 157insMTTTVP and HAV seropositivity protects against atopy but only in individuals with 157 insMTTTVP allele. The specification asserts that in some aspects the atopic disease is allergic rhinitis, atopic dermatitis, or asthma (see page 2, paragraph 6).

The specification asserts that polymorphisms in the coding region of human TIM1 include an insertion, 157insMTTTVP (allele 1), a deletion 195ΔThr, 157insMTTVP, T140A, V161A, V167I, T172A, and N258D (see paragraph 37, page 8-9) and assert that most of these variations are located within exon 3. The specification asserts that Tim gene sequence is other than human Tim-1, allele 1. The specification asserts that in combination with HAV seropositivity, allele 1 is protective for atopy and the presence is indicative that an individual may benefit from exposure to HAV for atopy treatment and/or prophylaxis and determination of the presence of the allele may be determined by various methods known in the art (see page 10, paragraph 42). Although determination of allele is routine in the art, predictably correlating an

allele to any type of atopic immunological disorder in any human individual is unpredictable and the specification does not predictably correlate each of these polymorphisms with any type of atopic immunological disorder in any human individual.

The specification teaches there are a number of methods that are available for analyzing nucleic acid for the presence of a specific sequence. The specification teaches that amplification with detectable labels, oligonucleotide ligation, hybridization to any array are available (see paragraph 53-54, 56, pages 13-14). However, the specification does not predictably correlate a method for diagnosis determining a predisposition to any type of atopic immunological disorder in any human by detecting "any" polymorphism within the TIM-1.

The specification demonstrates a working example of association between atopy and 157insMTTTVP in a cross-sectional study of 375 individuals who were tested for serologic evidence of atopy and prior HAV infection. The specification demonstrates that HAV infection protects against atopy but only in individuals with the 157insMTTTVP Tim-1 allele (see paragraph 194, pages 54-55). Although, table 1 of the specification demonstrates that HAV positive subjects with the 157insMTTTVP Tim-1 allele are associated with protection against atopy, table S3 and S4 demonstrate that 157insMTTTVP is predictably correlative for only the Caucasian population that is HAV positive and that are homozygous for the 157insMTTTVP allele. Table S4 demonstrates that neither the HAV negative or HAV positive population of Asians subjects is statistically relevant to diagnosis a predisposition to any immunological disorder or atopy and Table S3 demonstrates that the only statistically relevant data in the Caucasian subjects is for Caucasians subjects with HAV that are homozygous for

157insMTTTVP allele. The specification asserts that the African American sample size was too small to present separately (see paragraph 199, page 56).

The specification does not teach the association of any polymorphism, other than the 157insMTTTVP allele, in TIM-1 gene with the risk of developing any type of atopic immunological disorder. The specification does not teach an association of any polymorphism with an increased likihood of developing an atopic immunological disorder.

The following is unclear from the teaching in the specification. The specification does not teach which polymorphism of the TIM-1 gene is predictably correlative to diagnosing a predisposition to any atopic immunological disorder. The specification teaches only a statistically relevant association of 157insMTTTVP in Caucasian subjects that are homozygous for the allele that HAV positive and have protection against atopy. The specification does not teach an association with any other polymorphism with TIM-1 and any atopy, immunological disorder, or association with presence or absence of HAV. It is unclear which polymorphism would be predictive of diagnosing a predisposition to any atopic immunological disorder in "any" individual.

The specification envisions hypothetical situations where any polymorphism within the TIM-1 gene could determine the presence of an atopic immunological disorder. The specification appears to be conceiving of possible scenarios where the presence of any polymorphism in TIM-1 would indicate the presence – or absence – of any atopic immunological disorder, however, it is unclear how one of skill in the art would determine which polymorphism of TIM-1 gene would diagnosis atopy.

The unpredictability of the art, the state of the prior art, and the level of skill in the art

While the state of the art and level of skill in the art with regard to detection of a polymorphism in a known gene sequence is high, the level of unpredictability in associating any particular polymorphism with a phenotype is even higher. The level of unpredictability is demonstrated by the prior art, the post filing art, and the instant specification.

The prior art does not teach any association between any polymorphism in TIM-1 gene and predisposition in any individual for any type of atopic immunological disorder.

While the claims of the instant application are broad and encompass analysis of any human, the instant specification provides evidence only of a statistically significant association between the 157ins MTTTVP allele of TIM-1 of SEQ ID No. 22, and protection against atopy in Caucasians that are positive for HAV.

Because the claims are drawn to methods that encompass the analysis of any polymorphism of TIM-1 gene, it is relevant to note that there are multiple polymorphic positions identified in TIM-1. A Gene Card search of TIM-1 gene indicates that there are 135 SNPs of TIM-1 gene (see page 7 of Gene Card). The instant specification does not teach any association of these 135 polymorphisms with any type of atopic immunological disorder.

Additionally, the prior art teaches that there are many parameters that need to be evaluated prior to using a genetic test to determine a disease and that these parameters yield gaps in information that are needed to complete a thorough screening of a genetic test. Post filing art, Kroese et al. (Genetics in Medicine, vol 6 (2004), p. 475-480) teach genetic tests are heterogeneous in nature and the exact characteristics of a particular genetic test to be evaluated must be tightly defined. Kroese et al. teach that a particular genetic condition may be caused by

more than one gene and these variations may be due to deletions and insertions not detected by routine sequence methods. (see page 476, 2nd column, last paragraph). Kroese et al. teach that genetic test is shorthand to describe a test to detect a particular genetic variant for a particular disease in a particular population and for a particular purpose and that it should not be assumed that once the characteristics of a genetic test are evaluated for one of these reasons that the evaluation will hold or be useful for other purposes and all measures of the test performance should be presented with their 95% confidence intervals (see page 477, 1st column, 1st and 2nd full paragraph). Kroese et al. teach that the limitations of our genetic knowledge and technical abilities means that for the moment there are likely to be gaps in the information needed to complete a thorough evaluation of many genetic tests (see page 479, 2nd column, last paragraph). Additional post filing art reveals that most gene association studies are typically wrong. Lucentini (The Scientist, 2004, Vol 18, page 20) teach that it strikingly common for follow-up studies to find gene-disease associations wrong (see page 2, 1st paragraph). Lucentini teaches that two recent studies found that typically when a finding is first published linking a given gene to a complex disease there is only roughly a one-third chance that the study will reliably confirm the finding (see page 2, 3rd paragraph). Lucentini teaches that bigger sample sizes and more family-based studies, along with revising statistical method, should be included in the gene association studies (see page 3, 2nd paragraph). Based on the data presented in the specification and the prior art teachings, it is unpredictable to correlate any polymorphism within the TIM-1 gene with any type of atopic immunological disorder, as the specification does not teach a large sample size or confidence levels greater than 95% for every polymorphism of the TIM-1 gene or the association of TIM-1 with any type of atopic immunological disorder. The specification only

teaches a large sample size with statistically significant data for the analysis of an association between HAV positive subjects with the 157insMTTTVP allele in a Caucasian population.

Furthermore, the post filing art teaches the unpredictability of determining an association in different ethnical groups with any polymorphism in TIM-1 gene with atopy. Noguchi et al. (Genes and Immunity (2003) 4:170-173) teach that the seven different polymorphism within the TIM-1 gene, including two insertions and deletions were found not associated with the development of asthma in Japanese asthmatic families that showed strong evidence for linkage of atopic asthma (see page 172, right column, last paragraph). Noguchi et al. teach that no observation between hHAVcr-1(TIM-1) polymorphisms and atopic asthma in Japanese asthmatic families was associated and these polymorphisms may be related to susceptibility to hepatitis A infection and teach that further studies of different populations are needed to elucidate the role of polymorphisms in the development of atopic and infectious diseases (see page 172, 2nd column, last paragraph).

Applicant's own post-filing art, Umetsu et al. (Ann NY Acad Sci, 2004, 1029:88-93), teach that in the total population there was no association of the TIM-1 insertion (157insMTTTVP) with atopy. Umetsu et al. teach that if an individual had one or two copies of the insertion polymorphism in TIM-1, he or she was as likely to be atopic as those who had no copies of the insertion polymorphism, however when assayed for HAV seropositive and seronegative, it was found that a significant inverse association of the insertion and atopy. Umetsu et al. teach that the HAV seropositive subjects who had one or two copies of the insertion were much less likely to be atopic that those who had no copies and the HAV negative population was no associated with any protection against atopy. (see page 92, 1st full paragraph).

Thus, Umetsu et al. teach that the only individuals that are HAV positive are predictably correlative to protection against atopy in individuals that have the polymorphic insertion in TIM-1 gene.

Graves et al. (J Allerg Clin Immunol 2005, vol 118, pages 650-656) teach a study to evaluate multiple polymorphism in TIM1 gene and the association with atopy. Graves et al. teach association with atopy and one polymorphism, 15bp insertion/deletion of TIM-1 (see page 655, 1st column, 1st full paragraph). Graves et al. teach that in a Korean case control study increased risk for atopic dermatitis was found but not for asthma with the 15bp deletion of the TIM-1 gene (see page 655, 1st column, 1st full paragraph). Graves et al. teach analysis of seven different polymorphisms of TIM-1 gene and demonstrate that several polymorphisms are not statistically relevant, for example TIM1_1, 2, 5, and 7 (see table E2). Graves et al. teach that their findings need to replicated in other studies and the major limitation of the analysis is related to ethnic heterogeneity reflected in the Tucson population. Therefore, Graves et al. teach that multiple polymorphisms of TIM-1 gene that are not associated with atopy or immunological disorder and teach that further studies of an association of TIM-1 with atopy need to be completed.

The claims are broadly drawn to diagnosis of predisposition to any individual of various immunological disorders. The example presented in the specification provides an analysis of the 157insMTTTVP allele of TIM-1 gene with regard to HAV positive Caucasians subjects and atopy. The prior art teaches that confidence levels greater than 95% are necessary for predictably associating genetic tests with diseases. The instant specification shows the unpredictability in associating any polymorphism, including 157insMTTTVP allele of TIM-1

gene with any individual for any type of atopic immunological disorder. For example, table S3 demonstrates that 157insMTTTVP is not associated with atopy protection any individual that is not HAV positive and demonstrates that the 157insMTTTVP is not associated with atopy protection in every ethnic group (see table S4 and lack of African American analysis). Thus, based on the data presented in the specification and the prior art teachings, it is unpredictable to correlate any polymorphism within the TIM-1 gene with any type of immunological disorder, as the specification does not teach a large sample size or confidence levels greater than 95% for every polymorphism of the TIM-1 gene or the association of TIM-1 with any type of immunological disorder. The specification teaches a large sample size with statistically significant data for the analysis of an association between HAV positive subjects with the 157insMTTTVP allele in the TIM-1 in a Caucasian population for protection against atopy.

Quantity of Experimentation

Given the lack of guidance in the specification with regard to association of any polymorphism in the TIM-1 gene with any atopic immunological disorder in any individual along with the evidence in the art that demonstrates that not every polymorphism of TIM-1 gene is associated with an immunological disorder, the quantity of experimentation in this area is extremely large. The skilled artisan would have to perform an extremely large study and include different populations and familial studies for each of the polymorphisms of the TIM-1 gene (135 polymorphisms known) to determine if in fact there was either an association between the polymorphism in individuals and atopy. The results of such a study are clearly unpredictable as evidence by the applicant's own post filing art (which reflects the current state of the art) and the teachings in the specification with regard to correlating the 157insMTTTVP allele of TIM-1 with

different ethnic groups and HAV negative individuals to atopy much less any immunological disorder. Graves et al. teach that multiple polymorphisms of TIM-1 gene that are not associated with atopy or immunological disorder and teach that further studies of an association of TIM-1 with atopy need to be completed. Furthermore, Noguchi et al. teach that no observation between hHAVcr-1(TIM-1) polymorphisms and atopic asthma in Japanese asthmatic families was associated and these polymorphisms may be related to susceptibility to hepatitis A infection and teach that further studies of different populations are needed to elucidate the role of polymorphisms in the development of atopic and infectious diseases (see page 172, 2nd column, last paragraph). In the instant case, it would be unpredictable as to whether or not 157insMTTTVP would be responsible for determining the predisposition to atopy in any individual without also determining if the individual was HAV positive or negative.

In order to practice the invention as broadly as it is claimed, the skilled artisan would have to determine the sequence of the human TIM-1 in each individual and then determine which polymorphism would detect any type of immunological disorder. The skilled artisan would then have to screen variants to determine those that are associated with a susceptibility to any atopic immunological disorder in all populations. The skilled artisan would have to perform an extremely large amount of trial and error analysis in a large study to determine if such expression levels would predictable determine a susceptibility to all or any atopy. Given the lack of guidance in the specification and the post filing art with respect to accurately testing genetic diseases, such analysis is replete with unpredictable experimentation and is considered undue.

Response to Arguments

The response traverses the rejection on pages 11-23 of the response mailed 12/20/2006. The response asserts on page 13 that the amended claims encompass analysis for the presence of a polymorphism within the TIM-1 open reading frame or within regulatory sequences which immediately flank it and a polymorphism must be restricted to the TIM-1 gene with its attendant chromosomal location, consensus sequence, and structural features and thus the claim language excludes any sequence which are not so restricted. The examiner agrees that the claim language encompasses only polymorphism within the TIM-1 gene, however the specification is not enabled for the association of any polymorphism within the TIM-1 gene and the presence of the polymorphism which is indicative of atopic immunological disorder. The specification does not teach an association of any polymorphism within the TIM-1 gene and a predisposition to develop atopic immunological disorder. The specification asserts that the presence of the polymorphism, 157insMTTTVP is associated with protection against atopic immunological disorder but not teach an association of any polymorphism with developing an atopic immunological disorder.

The response asserts on page 13 that the specification describes atopic conditions which include asthma, allergic rhinitis, atopic dermatitis, and food allergies. The response asserts that the specification describes the TIM gene family and provides its chromosomal location, sequence organization, and sequence of commonly occurring human alleles. The response asserts that the specification provides everything there is needed such that an ordinary skilled artisan can identify polymorphic allelic variants of TIM-1 associated with atopic conditions and employ such polymorphisms for diagnostic purposes. This response has been thoroughly reviewed but not found persuasive. While identifying polymorphic allelic variants of a gene is

routine in the art, the ability to predictably correlate polymorphic variants with a disease is unpredictable. It is noted that patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable (*See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966), Stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion."*) Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. In instant case association of a polymorphic allele variant of TIM-1 with atopic conditions is not considered routine in the art and without sufficient guidance to a specific process of the associating a polymorphism to atopic immunological disorder to achieve a diagnostic outcome of predisposition to a disorder, the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh*, 17 USPQ2d 1714 (BPAI 1991). Therefore considering the state of the art and limited amount of guidance provided in the instant specification, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed. Furthermore, the specification only discloses the association of the polymorphism 157insMTTTVP and its protection against atopy. The specification does not disclose the presence of a polymorphism, and specifically, 157insMTTTVP and its association with an

increased likihood of a predisposition to atopic immunological disorder, to which the claims are drawn.

The response asserts on page 14, 1st paragraph, that under 35 USC 112, first paragraph the enablement requirement does not require or mandate a specific example be disclosed and the specification does not need to contain a working example if the invention is otherwise disclosed in such a manner that one skilled in the art would be able to practice the invention without undue experimentation. The examiner agrees that a working example is not required however the overwhelming evidence of the prior art demonstrates the unpredictability in the art and the specification does not disclose to one skilled in the art how to practice the claimed invention without undue experimentation to overcome the unpredictability in the art. For example, Lucentini teach that it strikingly common for follow-up studies to find gene-disease associations wrong (see page 2, 1st paragraph). Lucentini teaches that two recent studies found that typically when a finding is first published linking a given gene to a complex disease there is only roughly a one-third chance that the study will reliably confirm the finding (see page 2, 3rd paragraph). Lucentini teaches that bigger sample sizes and more family-based studies, along with revising statistical method, should be included in the gene association studies (see page 3, 2nd paragraph). In the instant specification, subgroup population studies demonstrate the unpredictability of associating the polymorphism, 157insMTTTVP with protection against atopy in different ethnic groups. For example, in the Asian subpopulation does not demonstrate a statistically significant association with protection against atopic immunological disorder and the presence of 157insMTTTVP (p value of .113 for homozygous and p value of .096 for heterozygous for HAV positive individuals) (See pg. 56, table S4). Therefore, the specification demonstrates that

confirming the finding of an association of a polymorphism with a disorder will not necessarily be confirmed in subpopulations and demonstrates the unpredictability of associating the presence of any polymorphism within the TIM-1 gene to predisposition to develop atopic immunological disorder.

The response asserts on page 14-15 that example 6 demonstrates experimental reduction to practice the claimed invention. The response asserts that the claims as amended are directed not to diagnosis of any type of immunological disease but to diagnosis of atopic immunological disorders in human individuals. The response asserts that example 6 demonstrates statistically significant interactions between a commonly carried TIM-1 allele and protective status toward atopy in human subjects. This response has been thoroughly reviewed but not found persuasive. Example 6 of the specification demonstrates a working example of determining an association with the polymorphism, 157insMTTTVP with protection against atopy however example 6 does not evaluate any other polymorphisms within TIM-1. Furthermore, example 6 does not evaluate diagnosis of atopic immunological disorder but evaluates protection against atopic immunological disorders and the presence of the polymorphism 157insMTTTVP. Example 6 presents statistically significant data for Caucasians who are HAV positive and are homozygous for the polymorphism 157inMTTTVP are protected against atopy (see table S3) however the data presented in table S4 demonstrates that Asians with the allele, 157insMTTTVP who are either positive or negative for HAV is not predictably association with protection against atopic immunological disorders because the data presented is not statistically significant (see table S4). Therefore example 6 does not provide experimental reduction to practice of the claimed invention, as example 6 does not provide data for any other polymorphisms, does not provide

data for predisposition for developing atopy immunological, as the data presented in example 6 is for protection against atopy, and demonstrates the unpredictability of the association of one polymorphism within different ethnic groups. Furthermore, the statistically significant data presented in example 6 is with regard to the protective effect of the polymorphisms in individuals who are Caucasians and are positive for HAV and the claims are not limited to a method of diagnosing predisposition to protection against atopy of in a hepatitis virus A positive Caucasian individual.

The response asserts on page 15 that the claims are not directed to a product consisting of TIM-1 sequences or probes but to a method of analyzing and using the same. The response further asserts that techniques for generating probes with specificity for any TIM-1 alleles are routine in the art. This response has been thoroughly reviewed but not found persuasive. The examiner agrees the techniques for generating probes with specificity for TIM-1 alleles is routine in the art. However, the claims are not drawn to a method of analyzing the TIM-1 sequence. The claims are drawn to a method of diagnosis a human individual's predisposition to an atopic immunological disorder by analyzing a polymorphism for the presence of a TIM-1 polymorphism. As such the claims require the knowledge of an association of polymorphism within the TIM-1 gene and atopic immunological disorders. The specification does not evaluate any TIM-1 polymorphism other than 157insMTTTVP and its association with atopic immunological disorders in an individual.

The response asserts on page 15, last paragraph, the reduction to practice may be an actual reduction to practice or a constructive reduction to practice. The response asserts that the instant specification in multiple experimental examples unambiguous evidence that the TIM-1

gene is associated with protection from atopy and the constructive reduction to practice by the present application provides a rationale for the selection of the TIM-1 gene as a diagnostic tool for multiple atopic immunological disorders and a means to effect such diagnosis using TIM-1 allele in clinically identified atopic individuals. This response has been thoroughly reviewed but not found persuasive. The specification provides evidence that the allele, 157insMTTTVP in Caucasians that are HAV positive is associated with atopy protection, however the data presented in the specification provides evidence that the polymorphism, 157insMTTTVP in HAV negative Caucasians and Asians individuals is not associated with diagnosis of atopy protection (see table S3 and S4, p values greater than .05) and therefore provides evidence that the ability to associate any polymorphism within the TIM-1 gene with diagnosis of atopic immunological disorder is unpredictable. The art provides further evidence of the unpredictability of associating a polymorphism within the TIM-1 gene with atopy. Graves et al. teach that multiple polymorphisms of TIM-1 gene that are not associated with atopy or immunological disorder and teach that further studies of an association of TIM-1 with atopy need to be completed. Additionally, Noguchi et al. teach that no observation between hHAVcr-1(TIM-1) polymorphisms and atopic asthma in Japanese asthmatic families was associated and these polymorphisms may be related to susceptibility to hepatitis A infection and teach that further studies of different populations are needed to elucidate the role of polymorphisms in the development of atopic and infectious diseases (see page 172, 2nd column, last paragraph) (see rejection above). Therefore, the evidence in the art coupled with the evidence in the specification demonstrates the unpredictability of associating any polymorphism in the TIM-1 gene with predisposition to developing an atopic immunological disorder in an individual.

Applicants assert on page 16 that the office action is wrong in the assertion that tables S3 and S4 demonstrate that 157insMTTVP is predictably correlative for only Caucasian population that is HAV positive and homozygous for the allele. The response asserts both tables report significant P vales for HAV + individuals and as such the 157insMTTTVP allele is predictably correlative for the group including seropostive heterozygous and homozygous individuals in both Caucasians and Asian populations. The response further asserts that the lack of presentation of African Americans is due solely to the small n value of the group and the statistical conclusion therein is valid for all included ethnicities. This response has been thoroughly reviewed but not found persuasive. It is noted that tables S3 and S4 present data for protection against atopy and do not provide evidence or data for the diagnosis of an individual's predisposition to develop an atopic immunological disorder by detecting the presence of a polymorphism in the TIM-1 gene, to which the claims are drawn. Table S4 demonstrates the Asian population that is HAV + with the 157insMTTTVP allele, that are homozygous has a p value of .113 and heterozygous have a p value of .096. Furthermore, the Asian population that is HAV – does not present any statistically significant data association with atopy protection. For the Caucasian population, table s3 presents no statistically significant data with the association of atopy or atopy protection and any TIM-1 allele as HAV – population has a p value greater than .05 and only demonstrates statistically significant data for HAV + population that is homozygous for atopy protection but not for developing atopy, to which the claims are drawn. In both tables S3 and S4, the column that is 1 vs. 0 allele demonstrates a p value greater than .05 and therefore the association of the heterozygous allele within the HAV + population is not statistically significant. Furthermore, the lack of presentation of African American due to a small sample size does not provide substantial

evidence that the association of 157insMTTTVP or any polymorphism within the TIM-1 gene, to which the claims are drawn, is predictably correlative with atopic immunological disorder in an African American population. It is noted, the claims are drawn to diagnosis of a human's predisposition to developing atopic immunological disorder by the presence of a polymorphism in the TIM-1 gene , which encompasses any human population with a polymorphism in the TIM-1 gene, this includes HAV positive population and the specification demonstrates on pg. 56, table S3 that Caucasians with a polymorphism in the TIM-1 gene, specifically 157insMTTTVP that are HAV positive are protected against developing atopy and therefore the data presented in the working examples contradicts the claimed invention.

Applicants assert on page 16 cont'd to page 17 that the specification teaches the use of a polymorphism in the TIM-1 gene to determine a statistical likelihood of vulnerability to an atopic immunological disorder, not the presence of absence thereof. The response asserts that it is nowhere cited or implied that the instant Application that every polymorphism of TIM-1 gene will carry predictive association with an atopic disease. The response asserts that the claimed method relies on techniques well known to the art in order to assay statistical association of any give polymorphism with an atopy presentation. This response has been thoroughly reviewed but not found persuasive. Although the specification does not imply or cite that every polymorphism of TIM-1 gene will carry predictive association with an atopic disease, the claims are drawn to a polymorphism in the TIM-1 gene and its association with atopic disease. The claims are not limited to a specific polymorphism within the TIM-1 gene and therefore encompass *any* polymorphism with the TIM-1 gene.. Furthermore the claims are not drawn to a screening or assaying method to determine if a polymorphism is associated with atopy, the claims require the

knowledge of the association of a polymorphism within TIM-1 gene and atopy and the specification does not enable the skilled artisan to associate polymorphisms within the TIM-1 gene and atopy.

The response asserts on page 17, 1st full paragraph that the skilled artisan would be able to determine which polymorphisms in the TIM-1 gene would diagnose atopy. The response asserts that populations of individuals suffering atopic conditions are routinely clinically identified and give the specification in which the important role of the TIM-1 gene in immunological response and atopic disorders is described and diagnostic conditions exemplified coupled with the knowledge in the art it would be no more than a matter of routine experimentation for one skilled in the art to association a polymorphism in TIM-1 with atopic conditions of interest and employ the claimed method to diagnose a predisposition to the atopic condition of interest. This response has been thoroughly reviewed but not found persuasive. As evidence in the specification exemplified in example 6 and the teaching in the prior art, the ability to predictably association a polymorphism within TIM-1 with an atopic disorder is unpredictable. Furthermore, as stated above, while identifying polymorphic allelic variants of a gene is routine in the art, the ability to predictably correlate the polymorphic variants with a disease is unpredictable. In the instant case, the specification is suggesting the role of TIM-1 in immunological response and atopic disease and suggesting that polymorphisms within this gene may be associated with an atopic disease, however the specification does not provide evidence that polymorphisms within TIM-1 gene in any population are associated with atopic disease. The specification asserts an association of one polymorphism with the TIM-1 gene with

protection against atopy however the specification does not demonstrate the presence of a polymorphism within the TIM-1 gene and predisposition to developing atopy.

The response asserts on page 18 that the specification has demonstrated 95% confidence intervals, as taught by Kroese. The response asserts that HAV+ individuals with 1 or 2, 2 or a single 157insMTTTVP are protected from atopy with p=.0005, p=.002, p=.004 and the critical findings of the analyses are presented in tables S3 and S4. This response has been thoroughly reviewed but not found persuasive. The claims are drawn to diagnosis of any individual by the presence of a polymorphism in TIM-1 gene. The specification does not demonstrate 95% confidence intervals for individuals who are not positive for HAV or have other polymorphism within the TIM-1 gene other than 157insMTTTVP. The specification demonstrates that individuals who are HAV – have a p value greater than .01, for example, p=.3777 for heterozygous allele 157insMTTTVP. Furthermore, the critical findings demonstrated in table S3 and S4 contradict the 95% confidence interval data presented in table 1. Table S3 and S4 demonstrate that the only data that has a 95% confidence interval is the Caucasian population who are positive for HAV and are homozygous for the 157insMTTTVP allele and this data is only for protection against atopy and not for predisposition to developing atopy.

The response addresses the recommendations of Lucentini on page 19 and assert the population displaying atopic conditions is large and diverse as evidence in the present specification and assert that the likihood of founder effects is small and the likihood of such effects reducing the informatively of the data in a study comprising multiple ethnic groups is small and the recommendations of Lucentini are satisfied with respect to the instant specification. It is noted that although the population is large and diverse that is presented in the

specification, the data presented in the subpopulation findings in the specification demonstrates that unpredictability of associating a polymorphism with atopic immunological disorder in any population. The critical findings demonstrated in table S3 and S4 demonstrate that the polymorphism is not associated with atopic immunological disorder in every population, as both Caucasians and Asians that are not HAV + who carry either the homozygous or heterozygous allele 157insMTTTVP furthermore the specification does not demonstrate a population of individuals with the 157insMTTTVP and their predisposition to develop atopy. The specification demonstrates that the recommendations of Lucentini suggesting a large, more diverse sample size is necessary to demonstrate an association with a gene and disorder as the large study presented in the specification demonstrates that subpopulations, those that are HAV negative and different ethnic groups will not have a protection against developing atopy with the presence of the polymorphism 157insMTTTVP.

The response addresses Noguchi et al. on page 20, 1st three paragraph. The response asserts that none of the polymorphisms identified by Nogushi were associated with asthma in the present experimental examples. The response further asserts that there is no contradiction between the results of Noguchi and those of the present example because the individuals assayed in the specification was not for familial asthma. The response asserts that it is nowhere implied or recited that every polymorphism in TIM-1 must carry predictive association with an atopic disease and the claimed method relies on techniques well known in the art to assess association of a polymorphisms with atopy. This response has been thoroughly reviewed but not found persuasive. It is noted that the claims are drawn to the presence of analyzing a polymorphism within the TIM-1 gene and the presence of a polymorphism is indicative of developing atopic

immunological disorder. The claims are drawn to atopic immunological disorders, which encompasses asthma including familial asthma and are drawn to the association of any polymorphism with the TIM-1, which encompasses the polymorphisms taught by Noguchi. It is noted that claim 1 and 7 recite "at least one TIM-1 polymorphism" and therefore encompass any polymorphism within the TIM-1 gene. Noguchi et al. demonstrates the unpredictability of associating any polymorphism in the TIM-1 with atopic immunological disorder. Noguchi et al. demonstrates polymorphisms in TIM-1 are not associated with asthma and further demonstrates that different populations are needed to elucidate the role of TIM-1 polymorphisms in atopic diseases (see pg. 172, 2nd column, last paragraph). Therefore, Noguchi et al. demonstrates that some polymorphism within TIM-1 are not associated with atopic immunological disease, such as asthma.

The response addresses Umetsu et al. on page 20. The response asserts Umetsu et al. confirm the results presented in the specification and there is no apparent contradiction between the result of Umetsu et al. and those of the present examples. This response has been thoroughly reviewed but not found persuasive. Umetsu provides evidence that individuals that are HAV negative are not associated with atopy (see pg. 92, 1st full paragraph). The claims are drawn to diagnosing any human for atopy by detecting the presence of a polymorphism in TIM-1. Claims 1, 4, 7, 20 and 23 are not limited to the population being HAV + or - and the specification demonstrates the unpredictability of associating any population with any polymorphism with atopy and Umetsu et al. provides further evidence of the unpredictability of associating any individual with atopy.

The response addresses Graves et al. on pages 20-21. The response asserts that none of the polymorphisms identified as not significantly associated with atopy by Graves et al. were found to be associated with atopy in the present examples and it is not recited or implied that every polymorphism of TIM-1 must carry predictive association with an atopic disease. This response has been thoroughly reviewed but not found persuasive. As stated above, claim 1 and 7 are broadly drawn to "at least one TIM1 polymorphism" and are not limited to specific polymorphisms and therefore the claims are broadly drawn to "any" polymorphisms within TIM-1 gene, which encompasses the polymorphisms studied by Graves et al. Graves et al. demonstrates that polymorphisms within TIM1 gene are not predictably associated with atopy. The response further asserts that Graves teach although a limitation of the analysis is reflected in the ethnic heterogeneity of the Tucson population similar results were replicated in children with two Caucasian parents, indicating significant association are unlikely to be related to population stratification as the result of ethnicity and the response asserts that the study does not cast doubt upon but rather substantiates the rationale and feasibility of the claimed method. This response has been considered but not found persuasive. Graves et al. asserts that their findings need to be replicated in other studies (see page 655, 1st column, last paragraph), which demonstrates their doubt on the results of the study and does not substantiate the rationale or feasibility of the claimed method. Furthermore, Graves et al. teach several different polymorphisms within TIM-1 gene that were not statistically relevant and not associated with atopy (see table E2) and further demonstrate that the 15bp deletion of the TIM-1 gene (see pg. 655, 1st column, 1st paragraph) was not associated with asthma but was associated with atopic dermatitis, which demonstrates the unpredictability of any atopy immunological disease and a polymorphism within the TIM-1

gene. Therefore, Graves et al. demonstrates the unpredictability of associating any polymorphism within TIM1 gene with atopic immunological disorder.

The response asserts that in support of the enablement of the claimed method, Gao et al. has been appended as exhibit A. It is noted that Gao et al. was not provided by applicants, however it is has been considered by the examiner. The response asserts that Gao et al. demonstrates that 157delMTTTVP were higher among patients with asthma compared with controls. The response asserts that Gao et al. demonstrate TIM 1 allelic variation is stasticially associated with atopic conditions in African American population. This response has been thoroughly reviewed but not found persuasive. Gao et al. demonstrate that African Americans that do not have the MTTTVP (see table II and pg. 987, 1st column, last paragraph) insertion are predictability associated with asthma which is the opposite of the claimed method. The claims are drawn to the presence of a polymorphism is associated with an individual predisposition to atopic immunological disorder (claim 1) and further limited to detecting the presence of MTTTVP. Therefore the claims are drawn to associating the insertion of MTTTVP with predisposition to atopic immunological disorder, whereas the teaching of Gao et al. teach that the deletion, not insertion of MTTTVP is associated with African American population and asthma (see pg. 987, 1st column, last paragraph). Furthermore, Gao et al. demonstrate that HAV seronegative population and the insertion variant is marginally associated with asthma (see pg. 985, 2nd column, last paragraph) which demonstrates the polymorphism is not statistically associated with atopy. Therefore Gao et al. provides evidence of the unpredictably of associating a polymorphism within TIM1 with atopic immunological disorder.

The response asserts that experimentation may be complex but does not necessarily make it undue. The response asserts that only experiments that need to be performed to enable the entire scope of the claim are those designed to assess the association of TIM-1 polymorphism with an atopic condition in a population of interest. The response asserts that the experimentation is routine. The response asserts that the only experimentation required to enable the claimed method is to confirm a statistical association of an allele in a population and this requires routine assay to determine and no undue experimentation is necessary. This response has been thoroughly reviewed but not found persuasive. As stated above, while identifying polymorphic allelic variants of a gene is routine in the art, the ability to predictably correlate the polymorphic variants with a disease is unpredictable. It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh*, 17 USPQ2d 1714 (BPAI 1991). Therefore considering the state of the art and limited amount of guidance provided in the instant specification, one skill in the art would have to engage in unpredictable, excessive and undue amount of experimentation to exercise the invention as claimed.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Claim Rejections - 35 USC § 112-Written Description

8. Claims 1, 4, 7-8 and 20-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the

relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection was previously presented in section 12 of the office action mailed 09/01/2006 and has been rewritten to address the amendment to the claims and newly added claims 20-23.

> Applicant is referred to the revised interim guidelines on written description published January 5, 2001 in the Federal Register, Volume 66, Number 5, page 1099-111 (also available at www.uspto.gov).

The rejected claims are broadly drawn to methods for diagnosing predisposition to any atopic immunological disorder comprising determining any polymorphism in any human individual (claim 1). The claims are broadly drawn to methods comprising the detection of a variety of nucleic acids, including any polymorphic variant of TIM-1 gene that is associated with any type of atopy. The claims are limited to probes that specifically bind to exon 3 of TIM-1 gene (claim 23) or probes that bind to MTTTVP sequence (claim 4 and 20), however the limitation of probes that specifically bind to a nucleic acid sequence or exon 3 does not limit the claims to detection of a specific polymorphism of TIM-1 gene as the claims merely require analyzing a biological sample with a probe that specifically binds to a nucleic acid sequence and this does not limit the polymorphism that is indicative of atopic immunological disorder. The claims merely require analyzing a probe that binds to a nucleic acid but the claims do not require the presence of the specific probe binding to the nucleic acid is indicative of predisposition to develop an atopic immunological disorder. The claims are further limited to steps of analyzing for the presence of HAV seropositivity wherein the seropositivity of an individual expressing an allele of TIM-1 comprising the amino acid sequence of MTTTVP is indicative of a reduced risk of developing atopy (amended claim 8 and newly added claim 22), however this recitation does

not further limit the detection of the specific polymorphism within the TIM-1 gene and its association with predisposition to atopic immunological disorder, claim 8 and 22, merely requires the additional detection of the MTTTVP allele and therefore, claim 8 and 22 broadly encompasses detection of any polymorphism in TIM-1 gene.

When the claims are analyzed in light of the specification, the instant invention encompasses methods comprising the analysis and detection of an enormous and wide variety of nucleic acid sequences. The claims are broadly drawn to a method that encompass a plurality of nucleic acids an extremely large genus of polymorphic variants of the TIM-1 gene with any nucleotide content (A or G or C or T) at any position within the TIM-1 gene. Thus the claims encompass the detection of any of different nucleic acids wherein the nucleic acid sequence is correlated with an association of disease. Nucleic acids of such a large genus have not been taught by the specification.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. The instant specification provides the sequence of SEQ ID No. 18, 20, 22, 24, 26, and 28. The specification also provides the amino acid sequence of TIM-1 as SEQ ID No. 19, 21, 23, 25, 27, and 29. The specification provides analysis of the insertion of the following amino acid sequence of MTTTVP at position 157 and indicating that this insertion is indicative of association of disease. The specification does not teach any association with any other polymorphic variation disclosed in the specification, for example deletion 195ΔThr, 157insMTTVP, T140A, V161A, V167I, T172A, and N258D that are indicative of association of atopic immunological disorders.

Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. other than nucleotide sequence, gene name, and specific polymorphic position), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, the specification provides only the polymorphic sequences of the human TIM1 gene (SEQ ID NO: 18, 20, 22, 24, and 26) and the encoded amino acid sequence (SEQ ID NO: 19, 21, 23, 25, 27). The specification does not provide any characteristics that would allow one to identify any other genes from another organism or any particular portions or fragments or variants of the disclosed sequence that would allow for the diagnosis of any type of atopic immunological disorder based on detection of the non-disclosed gene. Furthermore, the art discloses that there are 135 SNPs known for the TIM-1 gene (see GeneCard, page 7). Neither the specification nor the prior art teach an association with any of these SNPs with any type of immunological disorder or atopy.

Applicants' attention is directed to the decision in *In re Shokal*, 113 USPQ 283 (CCPA 1957) wherein is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. In re Soll, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189; In re Wahlforss et al., 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

In the instant application, because of the lack of any analysis regarding polymorphisms of the TIM-1 gene other than the insertion of the amino acid sequence of MTTTVP at position 157 of the amino acid sequence, one of skill in the art cannot envision the detailed chemical structure

of the nucleic acid encompassed by the claimed methods, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that such nucleic acids are part of the invention and reference to a potential method for identification. The particular nucleic acids are themselves required.

In conclusion, the limited information provided regarding the nucleic acids of the claimed methods is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of a method of diagnosis for the predisposition of immunological disorder in an individual by determining the presence of a polymorphism in TIM-1 other than methods using detection of the insertion of the amino acid sequence MTTTVP at position 157 of TIM-1.

Thus, having considered the breadth of the claims and the provisions of the specification, it is concluded that the specification does not provide adequate written description for the claims.

Response to Arguments

9. The response traverses the rejection on pages 23-26 of the response mailed 12/20/2006. The response asserts the specification defines the term TIM1 gene structurally on page 10, paragraph 41 and page 45, paragraph 167. The response asserts that figures 7-8 and sequence listings 17 to 39 provide ample sequence information. This response has been thoroughly reviewed and is found persuasive. The rejection with regard to not structurally defining the term "TIM-1" has been withdrawn, however the rejection has been maintained with regard to lack of description for the large genus of polymorphic variants of the TIM-1 gene and their association with a disease. The claims are drawn to an extremely large genus of polymorphic variants of the TIM-1 gene with any nucleotide content (A or G or C or T) at any position within the TIM-1

gene. Thus the claims encompass the detection of any one of different nucleic acids wherein the nucleic acid sequence is correlated with an association of disease. Nucleic acids of such a large genus have not been taught by the specification.

The response asserts on page 25, that modern array based methods frequently query thousands of genes and upon encountering a TIM-1 polymorphism in a population one of skill in the art is readily able to envision the necessary structure of probes suitable for use in the claimed method. The response asserts that the structure of the TIM gene family is established in detail in the specification and generalizable methods of preparing probes are robust commonplace and well known to the art. The response asserts that the amended claims encompass a method of analysis for the presence of polymorphisms using a probe that specifically binds under stringent conditions to the nucleic acid sequence of a TIM-1 gene. The response asserts that the claims are not directed to products consisting of TIM-1 sequence or probes and as such a specific polymorphism being probed by the instant method constitutes an object of analysis rather than a claimed product. This response has been thoroughly reviewed but not found persuasive. The examiner agrees that the claims are not drawn to products consisting of TIM-1 sequence or probes, however the claims require the knowledge that a polymorphism of TIM-1 gene is correlated to atopic immunological disorder. Furthermore, the claims are not drawn to a method of analysis but encompass a method of diagnosis by analyzing for the presence of a TIM-1 polymorphisms by contacting a biological sample comprising nucleic acids from an individual with a probe that specifically binds under stringent conditions to the nucleic acid sequence of TIM-1 gene wherein the presence of the polymorphism is indicative of an individual's predisposition to develop atopic immunological disorder. It is noted that the claims do not

require that the specific binding of a probe is indicative of predisposition to develop atopic immunological disorder, the claim require that the presence of a polymorphism is indicative of a predisposition to an atopic immunological disorder and the presence of a probe binding to a nucleic acid is not correlated with a specific polymorphism. Furthermore, the specification does not teach a representative number of polymorphisms within the TIM-1 gene that are associated with atopic immunological disorder and diagnostic of developing atopic immunological disorders. The specification discloses only one polymorphism, 157insMTTTVP that is associated with protection against developing an atopic immunological disorder in Caucasians that are HAV + (see example 6, pg.53-58) and the specification does not disclose a single polymorphism that when present in an individual is diagnostic of predisposition to developing atopy.

The response asserts on page 25 cont'd to page 26, that while there may be sequences within the genus defined by TIM-1 polymorphism that are not significantly associated with atopic immunological conditions the courts clearly taught that even in unpredictable arts the specification does not have to disclose every species of a genus that would work and every species that would not work. The response asserts that since one of skill in the art would recognize that a reasonable correlation is readily established by known methods between atopy and members of this genus, and since every species in the genus does not have to be tested for the genus to be enabled, extensive sequence disclosure or guidance regarding the active species in the genus does not have to be provided in order for a genus of this scope to be enabled. The examiner agrees that not every species needs to be disclosed, however a representative number of the large genus needs to be disclosed and the specification does not disclose a representative

number of TIM-1 polymorphisms that are associated with atopic immunological conditions. The specification merely discloses one polymorphism,157insMTTTVP, associated with protection against but not diagnostic of atopic immunological conditions, which is not a representative number of the large genus of TIM-1 polymorphisms. Furthermore the one polymorphism, 157ins MTTTVP disclosed by the specification is not associated with atopic immunological conditions in all populations. Therefore the specification has not described a representative number of polymorphic species of TIM-1 gene that are associated with atopic immunological disorders.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Conclusion

10. No claims are allowable.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sarae Bausch whose telephone number is (571) 272-2912. The examiner can normally be reached on M-F 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866) 217-9197 (toll-free).

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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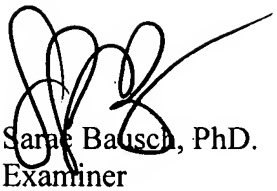

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Examiner
Art Unit 1634